during the reaction and was removed by washing the crude products with $Na_2S_2O_4$ solution prior to chromatography.

(C) With $PhIO_2$. A mixture of 0.6 mmol of $PhIO_2$ (142 mg) and 1.0 mmol (152 mg) of the substrate in CH_2Cl_2/MeOH (5:1, 12 mL) was stirred for 3 min. The purified product yield was 113 mg (75%) after chromatography.

(D) With $NaIO_4$. To 1.52 g (10 mmol) of the substrate dissolved in 50 mL of CH_2Cl_2 was added a solution of $NaIO_4$ (2.14 g, 10 mmol) in 10 mL H_2O. $PhCH_2NMe_3^+Cl^-$ (50 mg) was added to the mixture and the reaction mixture was stirred for 5 min. The product quinone from organic layer separated was isolated in 78% yield after chromatography. Without $PhCH_2NMe_3^+Cl^-$ vigorous stirring of the reaction with a magnetic stirrer gave the same results in 30 min.

The other quinones isolated, 2-methyl-1,4-benzoquinone,[15] 2,4-di-*tert*-butyl-1,2-benzoquinone,[16] 4-*tert*-butyl-1,2-benzoquinone,[17] 4-chloro-1,2-benzoquinone,[18] 3-methoxy-1,2-benzoquinone,[19] 2,5-di-*tert*-butyl-1,4-benzoquinone,[20] 2-*tert*-butyl-1,4-benzoquinone,[21] 1,4-naphthoquinone,[22] and bis(4-oxo-2,5-cyclohexadienylidene),[23] were identical with the known compounds.

Registry No. PhIO, 536-80-1; $PhIO_2$, 696-33-3; Bu_4NIO_4, 65201-77-6; $NaIO_4$, 7790-28-5; 4-*tert*-butyl-1,2-hydroquinone, 98-29-3; 3,5-di-*tert*-butyl-1,2-hydroquinone, 1020-31-1; 4-chloro-1,2-hydroquinone, 2138-22-9; 3-methoxy-1,2-hydroquinone, 934-00-9; 2-methyl-1,4-hydroquinone, 95-71-6; 2,3,6-trimethyl-1,4-hydroquinone, 700-13-0; 2-*tert*-butyl-1,4-hydroquinone, 1948-33-0; 2,5-di-*tert*-butyl-1,4-hydroquinol, 88-58-4; 1,4-dihydroxynaphthalene, 571-60-8; 4,4'-dihydroxybiphenyl, 92-88-6; 4-*tert*-butyl-1,2-benzoquinone, 1129-21-1; 3,5-di-*tert*-butyl-1,2-benzoquinone, 3383-21-9; 4-chloro-1,2-benzoquinone, 31222-02-3; 3-methoxy-1,2-benzoquinone, 60855-15-4; 2-methyl-1,4-benzoquinone, 553-97-9; 2,3,6-trimethyl-1,4-benzoquinone, 935-92-2; 2-*tert*-butyl-1,4-benzoquinone, 3602-55-9; 2,5-di-*tert*-butyl-1,4-hydroquinone, 2460-77-7; 1,4-naphthalenedione, 130-15-4; bis(4-oxo-2,5-cyclohexadienylidene), 494-72-4.

(15) Carstanjen, E. *J. Prakt. Chem.* **1881**, *23*, 423.
(16) (a) See ref 5. (b) Flaig, W.; Ploety, T.; Biergane, H. *Justus Liebigs Ann. Chem.* **1955**, *587*, 196.
(17) Teuber, H.-J.; Staiger, G. *Chem. Ber.* **1955**, *88*, 802.
(18) Kvalnes, D. E. *J. Am. Chem. Soc.* **1934**, *56*, 2487.
(19) Alder, E.; Magnusson, R. *Acta Chem. Scand.* **1953**, *13*, 505.
(20) Schulze, H.; Flaig, W. *Justus Liebigs Ann. Chem.* **1952**, *575*, 231.
(21) Glein, W. K. T.; Gaydasch, A. U. S. Patent 2 573 135, 1950; *Chem. Abstr.* **1952**, *46*, P3566*h*.
(22) Hannan, R. E.; Cason, J. *J. Org. Chem.* **1952**, *17*, 1058.
(23) König, K.-H.; Schulze, W.; Möler, G. *Chem. Ber.* **1960**, *93*, 554.

Selective Oxidation of Steroidal Allylic Alcohols Using 3,5-Dimethylpyrazole and Pyridinium Chlorochromate

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3,5-Dimethylpyrazole complexed with chromium trioxide has been used for the oxidation of alcohols to carbonyl compounds[1] and for effecting benzylic oxidation.[2] In the steroid series, this complex has also been successfully used for the allylic oxidation of Δ^5- and $\Delta^{8(14)}$-steroids to the corresponding ketones.[3,4] Pyridinium chlorochromate has recently found wide use in organic synthesis for the oxidation of primary and secondary alcohols to carbonyl compounds.[5] This reagent in methylene chloride containing 2% pyridine at 2–3 °C was reported to effect the high-yield selective oxidation of the allylic hydroxyl function of a number of steroidal alcohols.[6] We now report that $Py{\cdot}HCrO_3Cl$, when used in conjunction with DMP, is a convenient and useful reagent for the rapid and selective oxidation of allylic alcohols.

The selectivity of this reagent was indicated by its failure to significantly oxidize saturated primary and secondary alcohols relative to allylic alcohols. Treatment of **9**, **10a**, and **10b** with 3.0 equiv. of $Py{\cdot}HCrO_3Cl$ in methylene chloride containing an excess of DMP (2%) at 2–3 °C results in a >90% recovery of starting material. Under similar conditions, several steroidal allylic alcohols were successfully oxidized to the corresponding α,β-unsaturated carbonyl compounds (Table I).

When DMP and $Py{\cdot}HCrO_3Cl$ (3 equiv) were used, the diol **1** could be selectively oxidized to testosterone (**2**) in 87% yield. Under identical conditions, sterols **3a**, **5a**, and **7** were oxidized to the corresponding unsaturated ketones in high yield. Several of the substrates contained saturated secondary hydroxyl groups that were not concomitantly oxidized during the reaction. The allylic hydroxyl function in these sterols is in the quasi-equatorial configuration, which makes them more amenable to chromate oxidation. The quasi-axial allylic alcohol **3b** was selectively oxidized, giving a mixture of the 7-keto sterol and starting material. These results are consistant with the slower rate of oxidation reported for allylic alcohols with a quasi-axial configuration.[7] Increasing the amount of $Py{\cdot}HCrO_3Cl$ to 6 equiv resulted in an increased yield of product (91%), indicating the ability to successively oxidize allylic alcohols in either configuration. In constrast to these results, the oxidation of the quasi-axial allylic alcohol **5b** resulted in the formation of a complex mixture of oxidation products (observed by thin-layer chromatography) from which only a low yield of the 7-keto sterol **6** was obtained. These results are similar to those observed when **5b** was oxidized by $Py{\cdot}HCrO_3Cl$ in a 2% pyridine solution of CH_2Cl_2.[6] Undesired side reactions during the chromate oxidation of allylic alcohols have been reported by other workers.[7] Also, the susceptibility of **5b** and its ester derivatives to rearrangement has been observed previously during treatment with acid, Oppenauer oxidation, and pyrolysis.[8,9]

Manganese dioxide of controlled activity has been widely used for the selective oxidation of allylic and benzylic alcohols. Unfortunately, undesired side reactions, long reaction times, and failure of the oxidation of hindered hydroxyl functions have been reported.[7,10,11] Other chromate oxidizing reagents[12-14] and DDQ[10,15] have been reported to selectively oxidize benzylic and allylic alcohols with varying degrees of success. In general, these reactions

(1) E. J. Corey and G. W. J. Fleet, *Tetrahedron Lett.*, 4499 (1973).
(2) E. McDonald and A. Suksamrarn, *Tetrahedron Lett.*, 4425 (1975).
(3) W. G. Salmond, M. A. Barta, and J. L. Havens, *J. Org. Chem.* **43**, 2057 (1978).
(4) R. J. Chorvat and B. N. Desai, *J. Org. Chem.*, **44**, 3974 (1979).
(5) G. Piancatelli, A. Scettri, and M. D'auria, *Synthesis*, **245** (1982) and references cited therein.
(6) E. J. Parish and G. J. Schroepfer, Jr., *Chem. Phys. Lipids*, **27**, 281 (1980).
(7) H. O. House in "Modern Synthetic Reactions", W. A. Benjamin, Menlo Park, CA, 1972, pp 265–267.
(8) L. F. Fieser and G. Ourisson, *J. Am. Chem. Soc.*, **75**, 4404 (1953).
(9) B. N. Lutsky, J. S. Martin, and G. J. Schroepfer, Jr., *J. Biol. Chem.*, **246**, 6737 (1971).
(10) J. Fried and J. A. Edwards in "Organic Reactions in Steroid Chemistry", Vol. 1, Reinhold, New York, 1972, p 244.
(11) A. J. Fatiadi, *Synthesis*, 65, (1976).
(12) E. Santaniello and P. Ferraboschi, *Synth. Commun.*, **10**, 75 (1980).
(13) F. S. Guziec, Jr., and F. A. Luzzio, *J. Org. Chem.* **47**, 1787 (1982).
(14) X. Huang and C.-C. Chan, *Synthesis*, 1091 (1982).
(15) D. Burn, V. Petrow, and G. O. Weston, *Tetrahedron Lett.*, L9, 14 (1960).

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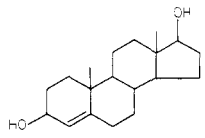
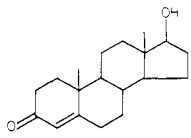
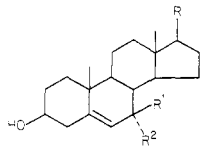
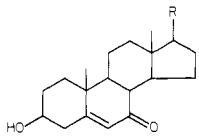
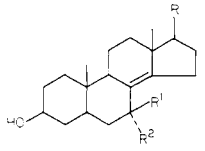
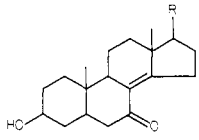
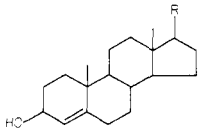
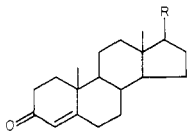
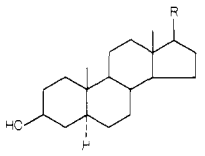
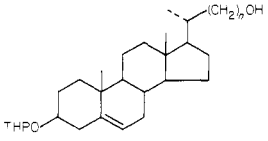
Table I. Selective Oxidation of Steroidal Allylic Alcohols to Ketones with Py·$HCrO_3Cl$ and DMP[a]

alcohol	conditions[b] (Py·$HCrO_3Cl$, equiv)	ketone product	yield,[c] %	recovered starting material, %
 1	3	 2	87	
 3a, R^1 = OH; R^2 = H	3	 4	89	
b, R^1 = H; R^2 = OH	3 (6)		61 (91)	29 (–)
 5a, R^1 = OH; R^2 = H	3	 6	86	10
b, R^1 = H; R^2 = OH	3 (6)		10 (–)	21 (9)
 7	3	 8	91	
 9	3			93
 10a, n = 1	3			90
b, n = 3	3			92

[a] R = C_8H_{17}. [b] The reactions were carried out in dichloromethane at 2–3 °C by using 0.6 mmol of alcohol. [c] Yield of isolated ketone product.

are characterized by moderate selectivity and extended reaction times. The observed selective oxidations of steroidal allylic alcohols by Py·$HCrO_3Cl$ and DMP (under basic conditions) at low temperatures and the ease of using this procedure offer a useful alternative to other reagents in oxidations of complex allylic alcohols.

Experimental Section

General Methods and Materials. Melting points were determined with an Electrothermal capillary apparatus and are uncorrected. Infrared spectra (KBr pellet) were recorded by using a Perkin-Elmer Model 580 spectrometer. Proton NMR spectra ($CDCl_3$ solvent) were obtained with a Varian EM-390 spectrometer using Me_4Si as an internal standard. Proton chemical shifts (δ) for the C-18 and C-19 angular methyl resonances were calculated by the method of Zurcher.[16] Ultraviolet spectra (ethanol solution) were recorded with a Cary 17 spectrometer. Mass spectral analyses were conducted on a DuPont 491 mass spectrometer. Gas–liquid chromatographic (GLC) analyses were performed on a Varian 3700 gas chromatograph using 3% OV-1 and 3% OV-17 columns (270 °C). Thin-layer chromatography (TLC) was carried out on plates of silica gel G (Analtech, Newark, DE) by using visualization of the components after spraying with molybdic acid.[17] Solvent systems for TLC analysis were 50% ether in toluene, 50% ethyl acetate in toluene, or 75% ether in hexane. Column chromatography employed silica gel (60–200 mesh) on columns that were 60 × 1.5 cm.

The preparation and evidence of structure of 5α-cholest-8-(14)-ene-3β, 7α-diol (**5a**),[18,19] 5α-cholest-8(14)-ene-3β,7β-diol (**5b**),[18,19] cholest-4-en-3β-ol (**7**),[6] 5α-cholest-3β-ol (**9**),[20] 3β-(tetra-

(16) R. F. Zurcher, *Helv. Chim. Acta*, **46**, 2054 (1963).

(17) F. F. Knapp, Jr., and G. J. Schroepfer , Jr., *Steroids*, **26** 339 (1975).

(18) M. Tsuda, E. J. Parish, and G. J. Schroepfer, Jr., *J. Org. Chem.*, **44**, 1282 (1979).

(19) L. G. Partridge, I. Midgley, and C. Djerassi, *J. Am. Chem. Soc.*, **99**, 7686 (1977).

(20) E. B. Hershberg, E. Oliveto, M. Rubin, H. Staeudle, and L. Kuhlen, *J. Am. Chem. Soc.*, **73**, 1144 (1951).

hydropyranyloxy)-23,24-dinorchol-5-en-22-ol (**10a**),[21] and 3-(tetrahydropyranyloxy)chol-5-en-24-ol (**10b**)[22] have been described previously. Androst-4-ene-3β,17β-diol (**1**) was prepared in 91% yield by reduction of testosterone (**2**) with $LiAl(O\text{-}t\text{-}Bu)_3H$ in THF.[6,23] Compound **1**, recrystallized from acetone–water, melted at 140–142 °C: IR ν_{max} 3400 1605, 1051 cm^{-1}; ^1H NMR δ 0.77 (s, 3 H, C-18-CH_3, calcd 0.78), 1.07 (s, 3 H, C-19-CH_3, calcd 1.08), 3.62 (t, 1 H, J = 8 Hz, C-17-H), 4.13 (m, 1 H, C-3-H), 5.29 (m, 1 H, C-4-H); MS, 290 m/e (relative intensity) (M, 3), 272 (100), 257 (7), 220 (10), 107 (27), 81 (38); single component on TLC in three solvent systems and on GLC. Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.58; H, 10.41. Found: C, 78.49; H, 10.52. Diols **3a** and **3b** were synthesized from the $LiAlH_4$ reduction of 3β-(benzoyloxy)cholest-5-en-7-one[3] followed by a column chromatographic separation of the epimeric mixture using a solvent gradient of ethyl acetate in toluene (**3a**, 78.3%; **3b** 13.7%); physical and spectral properties were consistant with those reported previously.[24] An authentic sample of **4** was prepared in 86% yield by the alkaline hydrolysis (Na_2CO_3 in CH_3OH[25]) of 3β-(benzoyloxy)cholest-5-en-7-one. Authentic samples of **6** and **8** were prepared by established methods.[18,26] 3,5-dimethylpyrazole, pyridinium chlorochromate, and testosterone were obtained from the Aldrich Chemical Co. All isolated reaction products and starting materials were compared with authentic compounds (TLC and/or GLC, IR, NMR, and MS). Elemental microanalyses were carried out by Galbraith Laboratories. Reactions were conducted under an atmosphere of dry nitrogen.

General Oxidation Procedure. Pyridinium chlorochromate (3 equiv, 388 mg, 1.8 mmol or 6 equiv, 776 mg, 3.6 mmol) was added to a solution (50 mL) of the sterol (0.60 mmol) in a mixture of CH_2Cl_2 and 3,5-dimethylpyrazole (2%, 10.4 mmol) at 2–3 °C. After stirring for 30 min under nitrogen, a saturated NaCl solution was added and the mixture was thoroughly extracted with $CHCl_3$. The resulting extracts were dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness under reduced pressure to give a brown residue, which was subjected to column chromatography using a solvent gradient of ether in toluene (**2** required a gradient of ether in hexane). The purified material was recrystallized from acetone-water to give the products shown in Table I and described below.

Compound **1** formed testosterone (**2**): 151 mg (87%); mp 154–155 °C [lit.[27] 154.5–155.5 °C]; IR ν_{max} 1612, 1665, 3400, 1232, 1058 cm^{-1}; UV λ_{max} 238 nm, (ϵ16 000) [lit.[27] λ_{max} 238 nm]; ^1H NMR δ 0.79 (C-18-CH_3, calcd 0.80), 1.20 (C-19-CH_3, calcd 1.21), 3.64 (m, 1 H, C-17-H), 5.69 (m, 1 H, C-4-H); MS, 288 m/e (relative intensity) (M, 25), 270 (M – H_2O, 4), 246 (42), 302 (17), 147 (29), 124 (100); single component on TLC and GLC.

Oxidation of **3a** gave **4** (214 mg, 89%) melting at 171-172 °C [lit.[28] mp 170–172 °C]: IR ν_{max} 1658, 1678, 1068, 3250 cm^{-1}; UV λ_{max} 238 (ϵ12 500) [lit.[28] λ_{max} 238 nm]; ^1H NMR δ 0.69 (s, 3 H, C-18-CH_3, calcd 0.69). 1.20 (s, 3 H, C-19-CH_3, calcd 1.20), 3.69 (m, 1 H, C-3-H), 5.71 (m, 1 H, C-6-H); MS, m/e (relative intensity) 400 (M, 36), 382 (M – H_2O, 30), 367 (M – CH_3 – H_2O, 4), 269 (M – H_2O – side chain, 3), 192 (35), 187 (38) 174 (100); single component on TLC and GLC.

Oxidation of **3b** with 3 equiv of Py·$HCrO_3Cl$ gave **4** in 61% (147 mg) and recovered starting material **3b** in 29% (70 mg) yield. Reaction with 6 equiv of the oxidant resulted in a 91% (219 mg) yield of **4**; mp 171–172 °C. The TLC, GLC, IR, UV, NMR, and MS were identical with those of **4** as prepared from **3a**.

Compound **5a** formed ketone **6**: 207 mg (86%); mp 129–131 °C (lit. mp 129–131 °C,[18] 129–130 °C[29]]; IR ν_{max} 3400, 1670, 1590, 1045, 948, 846 cm^{-1}; UV λ_{max} 262 nm (ϵ 8500) [lit. λ_{max} 262,[18] 261[29]]; ^1H NMR δ 0.82 (s, 3 H, C-18-CH_3, calcd 0.83), 0.94 (s, 3 H, C-19-C_3, calcd 0.97), 3.65 (m, 1 H, C-3-H); MS, m/e 400 (relative intensity) (M, 100), 385 (M – CH_3, 8), 382 (M – H_2O, 13), 367 (M – CH_3 – H_2O, 2), 315 (6), 287 (M – side chain, 21), 273 (11), 269 (M – H_2O – side chain, 8), 259 (10), 245 (11), 234 (50), 232 (9); single component on TLC and GLC.

Oxidation of **5b** with 3 equiv of Py·$HCrO_3Cl$ produced a complex mixture of oxidation products (TLC analysis), which yielded 10% (24 mg) of **6**: mp 129–131 °C; TLC, GLC, IR, UV, NMR, and MS were identical with those of **6** as prepared from **5a**. Continued column elution produced 21% (51 mg) of starting material **5b**. Reaction with 6 equiv of the oxidant resulted in a 9% (22 mg) recovery of **5b**.

Compound **7** was oxidized to **8**: 210 mg (91%); mp 80–81.5 °C [lit. mp 80–81.5 °C,[6] 81–82 °C[26]]; IR ν_{max} 1684, 1621, 872 cm^{-1}; ^1H NMR δ 0.72 (s, 3 H, C-18-CH_3, calcd 0.73), 1.20 (s, 3 H, C-19-CH_3, calcd 1.19), 5.89 (s, 1 H, C-4-H); UV λ_{max} 242 nm (ϵ 17 000) [lit.[6,25] λ_{max} 242]; MS, m/e (relative intensity) 384 (M, 100), 369 (M – CH_3, 15), 343 (40), 299 (14), 271 (M – side chain, 17), 261 (46), 229 (64); single component on TLC and GLC.

Attempted oxidation of the nonallylic sterols **9**, **10a**, and **10b** using 3 equiv of Py·$HCrO_3Cl$ resulted in the recovery of the respective starting materials in 93% (216 mg), 91% (341 mg), and 92% (245 mg).

Acknowledgment. This research was supported in part by a Schering-Plough Corporation Grant for Research Corporation and by Auburn University (Grant-in-Aid 2-12565).

Registry No. **1**, 1156-92-9; **2**, 58-22-0; **3a**, 566-27-8; **3b**, 566-26-7; **4**, 566-28-9; **5a**, 40878-67-9; **5b**, 65164-27-4; **6**, 566-29-0; **7**, 517-10-2; **8**, 601-57-0; **9**, 80-97-7; **10a**, 34026-84-1; **10b**, 66414-43-5; 3β-(benzoyloxy)cholest-2-en-7-one, 6997-41-7; pyridinium chlorochromate, 26299-14-9; 3,5-dimethylpyrazole, 67-51-6.

(21) Y. Fujimoto, M. Morisaki, and N. Ikekawa, *J. Chem. Soc.*, Perkin *Trans. 1*, 2302 (1975).
(22) M. Morisaki, M. Shibata, C. Duque, N. Imamura, and N. Ikekawa, *Chem. Pharm. Bull.*, **28**, 606 (1980).
(23) E. J. Parish and G. J. Schroepfer, Jr., *J. Labelled Compds. Radiopharm.*, **18**, 1429 (1981).
(24) J. I. Teng, M. J. Julig, L. L. Smith, G. Kan, and J. E. van Lier, *J. Org. Chem.*, **38**, 119 (1973).
(25) E. J. Parish and G. J. Schroepfer, Jr., *J. Org. Chem.*, **45**, 4034 (1980).
(26) L. F. Fieser, *J. Am. Chem. Soc.*, **75**, 5421 (1953).
(27) L. Ruzicka and A. Wettesein, *Helv. Chim. Acta*, **18**, 1264 (1935).
(28) S. Bergstrom and O. Wintersteiner, *J. Biol. Chem.* **141**, 597 (1941).
(29) L. F. Fieser, K. Nakanishi, and W.-Y. Huang, *J. Am. Chem. Soc.*, **75**, 4719 (1953).

Reexamination of the Reaction of Triethyl Phosphite with *o*-Hydroxybenzyl Alcohol

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In a brief series of papers, Ivanov and co-workers[1] investigated the reaction of *o*-hydroxybenzyl alcohol (**1**) with trialkyl phosphites (Scheme I), particularly triethyl phosphite (**2**). From kinetic and IR data, they concluded that the reaction proceeded according to path 1, either in the absence of solvent or in DMF. While eliminating quinone and cyclic phosphite **5** structures as primary products, they concluded that the reaction mixture "evidently"[1d] contains **3**, which cyclizes to **4** during distillation and workup.

More recently, Miles et al.[2] in a discussion of one of Ivanov's earlier papers,[1c] proposed that the reaction of **1** with **2** did indeed proceed via **5** (path 2), which then rearranged to **4**. The rearrangement of **5** to **4** is reminiscent of an Arbuzov-type reaction. While the literature is replete

(1) (a) B. E. Ivanov and A. B. Ageeva, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 226 (1967); *Chem. Abstr.*, **67**, 11538*r* (1967); (b) B. E. Ivanov and L. A. Valitova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1087 (1967); *Chem. Abstr.*, **68**, 39723*s* (1968); (c) A. B. Ageeva and B. E. Ivanov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1494 (1967); *Chem. Abstr.*, **68**, 39738*a* (1968); (d) B. E. Ivanov, A. B. Ageeva, A. G. Abul 'Khanov, and T. A. Zyablikova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1912 (1969); *Chem. Abstr.*, **72**, 21110*n* (1970).
(2) J. A. Miles, R. C. Grabiak, and C. Cummins, *J. Org. Chem.*, **47**, 1677 (1982).

0022-3263/83/1948-4768$01.50/0